REMARKS

Claims 5, 6, 8, 10, 12, 14, 15, and 17-19 are pending in the application. The restriction requirement set forth in the prior Office Action has been withdrawn and all pending claims have been examined on the merits. Claims 5 and 10 are objected to, claims 5, 6, 14, and 17-19 are rejected under 35 U.S.C. § 112, second paragraph, claims 5, 6, 8, 10, 12, 14, 15, and 17-19 are rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 102, and claims 5, 6, 8, 10, 12, 14, 15, and 17-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting. Applicants address each of the rejections as follows.

As an initial matter, Applicants would like to thank Examiners Akhavan and Sullivan for the personal interview conducted with Applicants' representative, Chalin A Smith, on July 20, 2005.

Claim Amendments

Claims 5, 8, and 14 have been amended to recite the phrase "granulocyte-colony stimulating factor," which is the definition for G-CSF. Support for this amendment is found, for example, page 14, line 15, to page 15, line 3, of the English language specification. Claims 5, 8, and 14 have also been amended to replace the term "part" with the term "domain." Support for this amendment may be found, for instance, at page 6, line 13, to page 7, line 2, of the English language specification and in Example 1. Claim 10 has been canceled. In view of the cancellation of claim 10, the dependency of claim

15 has been amended. Claim 14 has been amended to be directed to a "pair of co-transformed vectors." Support for the amendment to claim 14 may be found, for example, at page 6, line 25, to page 7, line 2, of the English language specification. No new matter has been added by the present amendments.

In addition, new claims 20-24 have been added. New claims 20-24 find support, for example, at page 5, lines 14-17, and at page 6, lines 2-12, of the English language specification, and include no new matter.

Claim Objections

The Office objected to claims 5 and 10 for reciting "G-CSF" without setting forth the corresponding definition. Claim 10 has been canceled and, therefore, the objection to this claim is moot. Applicants submit that the present amendment to claim 5 overcomes this basis for objection.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 5, 6, 14, and 17-19 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Office asserts that the term "the G-CSF" in claim 5 lacks antecedent basis, and that "it is unclear whether the deleted region is in the extracellular domain of [the cytokine] G-CSF or of G-CSF Receptor." The Office further asserts that the limitation "part thereof" in claim 5 is vague and indefinite because "it is unclear whether it is directed to the extracellular portion(s) that is deleted or some

other region in the extracellular region."

Claim 5 has been amended to refer to a granulocyte-colony stimulating factor receptor or a proliferation-inducing domain of the granulocyte-colony stimulating factor receptor. In view of these amendments, Applicants submit that the § 112, second paragraph, rejection of claim 5, and its dependent claims, should be withdrawn.

In addition, the Office continues to object to use of the term "vector system" in claims 14 (and claims 18-19, which depend from claim 14) based on the assertion that "the term 'system,' as used in the claims or in the specification, implies additional steps, processes, elements or components, which remain undefined and indefinite." To expedite prosecution, claim 14 has been amended to be directed to "a vector system comprising a pair of co-transformed vectors." Applicants submit that this basis of the indefiniteness rejection should also be withdrawn[1].

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 5, 6, 8, 10, 12, 14, 15, and 17-19 stand rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description in the specification. In particular, the Office asserts (page 6):

> [T]he claims are directed to a genus of nucleic acid structures (i.e., vector molecules) encoding fusion proteins comprising *any* cytokine receptor or *any* proliferation-inducing portions of *any* cytokine receptor fused to *any* ligand-binding domain of *any* steroid hormone, with the functional

[1] In addition, Applicants note that the above amendments were presented in the July 20, 2005 interview and that, in the interview summary, the Office notes: "The proposed amendments appear to overcome the 112, second paragraph ... rejection."

> correlation of selective ligand-induced expansion (i.e., proliferation) of cells via the cytokine receptor portion of the fusion protein. (Emphasis original)

And (page 9):

> [G]iven the enormous breadth of the genus of fusion molecules encompassed by the rejected claims, and given the limited description from the instant specification of such fusion molecules, the skilled artisan would not have been able to envision a sufficient number of specific embodiments to describe the broadly claimed genus.

The Office also cites several references (Capon et al., U.S. Patent No. 5,837,544; Nakabeppu et al., Mol. Cell. Biol. 13:4157-4166, 1993; Horst Ibelgaufts' COPE: Cytokines Online Pathfinder Encyclopaedia; Fukunaga et al., Proc. Natl. Acad. Sci. USA 87:8702-8706, 1990; Bazan, Proc. Natl. Acad. Sci. USA 87:6934-6938, 1990; Fukunaga et al., EMBO J. 10-2855-2863, 1991; Taga et al., FASEB J. 7:3387-3396, 1993; and Cytokines Web: Cytokine Receptor Classification According to Domain Composition) in support of the assertion that the knowledge in the art does not provide sufficient relevant information for the skilled artisan to envision a sufficient number of specific embodiments to describe the broadly claimed genus.

Applicants submit that the present claims, as amended, are free of this basis for rejection. As detailed below, Applicants note that the present claims are not directed to fusion proteins containing any cytokine receptor, but rather a granulocyte-colony stimulating factor (G-CSF) receptor. Not only does the application as filed describe fusion proteins containing a G-CSF receptor, but the specification also describes a fusion protein containing a G-CSF receptor having a deletion in the extracellular domain.

In particular, claim 5, as amended, is directed to a vector including a gene

encoding a fusion protein containing (a) a first polypeptide and (b) a second polypeptide. The first polypeptide includes a ligand binding domain of a steroid hormone receptor that, upon ligand binding, dimerizes, and the second polypeptide includes a granulocyte-colony stimulating factor receptor in which a portion of the extracellular domain has been deleted, or a proliferation-inducing domain of the granulocyte-colony stimulating factor receptor, and imparts proliferation activity to a cell upon the dimerization of the first polypeptide. Similarly, claims 8 and 14 require the proliferation-inducing domain to be a domain of a G-CSF receptor. As such, the present claims, as amended, are not directed to any proliferation inducing portions of any cytokine receptor, but rather recite particular portions of a G-CSF receptor.

The specification, for instance, in Examples 1 to 3, describes G-CSF receptor proteins encompassed by the present claims, including fusion proteins having a deletion in the extracellular domain while retaining the proliferation-inducing portion. In particular, the specification describes GCR Δ (5-195)/ER which is a fusion protein of the G-CSF receptor and the estrogen receptor in which a portion of the G-CSF receptor extracellular domain has been deleted. As shown in Example 3, cells expressing a gene encoding GCR Δ (5-195)/ER proliferated in response to estradiol stimulation. As such, Applicants submit that the specification describes the second polypeptide recited in the present claims.

Moreover, the genus of G-CSF receptors is not widely variable. On this point, Applicants direct the Office's attention to the enclosed copy of Larsen et al. (J. Exp. Med.

172:1559-1570, 1990; "Larsen;" Exhibit 1). Larsen teaches that the human and murine G-CSF receptor sequences are highly conserved (see, e.g., the top of the left column on page 1564). Further, Applicants note that the murine G-CSF receptor sequence described in the specification was obtained from a murine cDNA library using human G-CSF receptor cDNAs as probes. Clearly, the human and murine G-CSF receptor sequences are highly related and one skilled in the art would expect the sequences of other G-CSF receptors to also be highly homologous to the human and murine sequences.

In addition, Applicants submit that the skilled artisan would readily recognize which portion of a receptor is the extracellular domain. For example, simply by comparing amino acid sequences, a skilled artisan would recognize whether an extracellular domain contains a deletion. In view of the above, Applicants submit that the genus of the G-CSF receptors recited in the present claims is clearly defined.

Turning to the ligand binding domains of steroid hormone receptors recited in the claims, it is Applicants' understanding, based on the Office's comments made to Applicants' representative during the July 20, 2005 interview, that the present written description rejection is not directed to the genus of steroid hormone receptors.

Nonetheless, Applicants note that ligand-binding domains of steroid hormone receptors find adequate written description in the specification as filed. With respect to a ligand-binding domain the English language specification, at page 6 (lines 2-7), teaches:

> Any ligand can be used in the present invention as long as it acts on a specific protein to cause association of the protein, but a steroid hormone is preferable. Examples of the steroid hormone include estrogens, androgens, progesterone, glucocorticoids, and mineral corticoids. They are used in combination with

their respective receptor proteins.

Given this passage of Applicants' specification, there can be no doubt that Applicants have satisfied the written description requirement for ligand-binding domains of steroid hormone receptors, and that Applicants have unambiguously described their invention so as to reasonably convey to persons skilled in the art that the inventors possessed the subject matter in question.

In addition, with respect to the issue that Applicants have not described a representative number of species of the claimed genus, Applicants point out that "[r]epresentative examples are not required by the statute and are not an end in themselves." *In re Robins,* 429 F.2d 452,457 (CCPA 1970). Rather, Applicants' specification "must 'convey clearly' to those skilled in the art to whom it is addressed ... the information that [the inventor] has invented the specific subject matter later claimed." *Martin v. Mayer,* 853 F.2d 500, 505 (Fed. Cir. 1987). In this regard, Applicants note that the claimed groups of compounds do not differ radically from each other and the examples found in the specification identify the group broadly to the skilled worker. *In re Grimme*, 274 F.2d. 949, 952 (CCPA 1960). Applicants naming of their claimed generic fusion proteins is therefore sufficient to satisfy the written description requirement. Furthermore, the case law is clear that "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every species." *Id.* In this case, Applicants' specification and specific examples, which teach how to select and recombine appropriate DNAs, are adequate to show those

skilled in the art how the claimed invention is to be practiced.

Further, "it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." See *Capon v. Eshhar*, 418 F.3d 1349,1359, citing *In re Angstadt*, 537 F.2d 498,504 (CCPA 1976). No evidence currently made of record in this case questions the enablement of Applicants' claimed invention. Moreover, to the extent the Office relies on Bazan, Fukunaga, Ibelgaufts, Taga, and Cytokines Web as evidence of unpredictability of cytokine receptors, Applicants note that identifying inoperable fusion proteins is accomplished using routine screening methods known in the art when the application was filed. Moreover, Applicants' disclosure provides considerable direction and guidance on how to practice their invention and presents working examples, aiding the skilled worker to weed out inoperable constructs. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known. Applicants' specification clearly characterizes the claimed generic invention. Any experimentation needed to practice the invention would not be considered undue.

In sum, for all the above reasons, Applicants submit that the specification as filed fully describes the invention encompassed by the present claims, as amended. The written description rejection should be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 8, 12, 14, 15, 17, and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nakabeppu et al. (Mol. Cell. Biol. 13:4157-4166, 1993; "Nakabeppu") and claims 5, 6, 8, 10, 12, 14, 15, 17, and 19 are rejected under 35 U.S.C. § 102(e) as being anticipated by Capon et al. (U.S. Patent No. 5,838,544; "Capon"). As noted above, claim 10 has been canceled and the rejection of this claim is moot. Applicants submit that the present claims are not anticipated by the cited references.

Nakabeppu et al.

The Office asserts (page 16):

> Nakabeppu et al. teach proliferative activation in cells wherein proliferation is induced by cell transfection with a vector encoding a fusion protein where the estrogen HBD [hormone binding domain] is linked to the cytokine *FosB*. *FosB* intrinsically comprises dimerization domains. (Citations omitted.)

To anticipate a claim, a prior art reference must disclose each and every element claimed. The claims, as amended, require the combination of a ligand-binding domain of a steroid hormone receptor and a G-CSF receptor that imparts proliferation activity to a cell. As the Nakabeppu fails to disclose this combination, Nakabeppu does not anticipate the present claims[2].

[2] In the summary of the July 20, 2005 interview, the Office notes that the proposed amendments appear to overcome the Nakabeppu prior art rejection.

Capon

The Office asserts (page 17):

> [Capon] teaches a chimeric constructs [sic] encoding a ligand-binding domain and a proliferation signaling domain (PSD), as well as vectors and cells containing said constructs, with or without exogenous genes.
>
> * * *
>
> [T]he chimeric construct can comprise an inducer-responsive clustering domain (ICD), i.e. hormone receptor domain, which upon binding the inducer or ligand will dimerize or cluster ... ICD domains can be eukaryotic steroid receptor molecules, including estrogen, progesterone, androgen ... In addition, the PSD portion of the chimeric construct can be the transducing domains (i.e., proliferation domains) of cytokine receptors, including IL-2 ... Further the PSD can be G-CSF.

Applicants disagree, noting that Capon fails to disclose the particular fusion proteins recited in the present claims.

The M.P.E.P. § 2132.02 makes clear that

> A genus does not always anticipate a claim to a species within the genus. However, when the species is clearly named, the species claim is anticipated no matter how many other species are additionally named. *Ex parte A,* 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990)
>
> * * * * *
>
> When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

In this case, Applicants respectfully submit that Capon's broad disclosure of a genus of chimeric receptor proteins, composed of any number of distinct domains, is analogous to a disclosure of a generic chemical formula having a wide range of possible substituents so as to encompass a vast number of compounds. As such, a species falling within the scope of Capon's genus but not explicitly named therein can only be anticipated *if* one of ordinary skill in the art could "at once envisage" the species of the claimed invention. Applicants respectfully submit that this is not the case; rather, arriving at the claimed combination of elements is the equivalent of finding a needle in a haystack.

Capon fails to clearly name applicants' claimed constructs

In this case, Capon not only fails to disclose the claimed steroid hormone receptor:G-CSFR (SHR:G-CSFR) fusions, but also fails to disclose the preferred species; estrogen receptor:G-CSFR (ER:G-CSFR) fusions. Instead, Capon broadly describes a vast genus of chimeric proliferation receptor proteins composed of at least two domains, namely an intracellular inducer-responsive clustering domain (ICD) and a proliferation signaling domain (PSD). See abstract and Figure 1(e). On this basis alone, Capon does not anticipate Applicants' claimed invention.

Capon's chimeric proteins are neither sufficiently limited nor well delineated

In order to arrive at Applicants' claimed species of chimeric protein (i.e., a ligand binding domain of a steroid receptor linked to a proliferation inducing domain of a G-CSF receptor), one must judiciously choose from Capon's vast list of alternatives and

possible permutations to arrive at the particular combination of discrete substituents claimed. For example, Capon describes the ICD as including but not limited to "immunophilins (e.g., FKBP), cyclophilins, and steroid receptors." (col. 7: 11-15). However, there is no direction in Capon to select a steroid hormone receptor, much less an estrogen receptor, as the ICD. In fact, when one looks to the preferred embodiments to determine which species can be "at once envisaged" and, therefore, anticipated, one finds the examples limited to FKBP.

Regarding the PSD, Capon states that the PSD may be selected from the cytokine/hematopoietin receptor superfamily or, alternatively, may be obtained from any member of the Janus or JAK eukaryotic family of tyrosine kinases. The listing of possible PSDs extends from col. 8, line 40 to col. 11, line 28, encompassing a vast number of potential substituents. However, of the cytokine family, only IL receptors are described in any detail. Moreover, the only combination of ICD and PSD described in the Examples includes domains from FKBP and ILR (see Example 7(f), (g)).

Given the vast number of possible combinations encompassed within this generic teaching and the fact that none of the preferred or exemplary embodiments discussed reference either the selection of a steroid hormone receptor (SHR) or a granulocyte-colony stimulating factor receptor (G-CSFR) in particular, much less the specific combination of the two, it is clear that one skilled in the art would not have immediately arrived at the particular combination claimed herein. As one skilled in the art would not have "at once envisaged" the embodiments of the pending claims, it is clear that these

claims cannot be anticipated by the Capon reference. As such, this rejection should be reconsidered and withdrawn.

Provisional Obviousness-Type Double Patenting

Claims 5, 6, 8, 10, 12, 14, 15, and 17-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, 10-14, 16-18, and 20 of co-pending Application No. 10/100,471 ("the '471 application"). In particular, the Office asserts (page 19):

> [B]ut for semantic changes and the order of the terms such as "vector" and "fusion protein" the claims are directed to patentably indistinguishable subject matter.

As an initial matter, Applicants note that the instant application is a divisional application of 09/142,305 (" the '305 application"), which is also a parent application of the '471 application. In the '305 application, the Office issued a restriction requirement asserting that claims to a fusion protein were patentably distinct from claims to a vector, cell, and kit. (A copy of the restriction requirement and the relevant claims is enclosed as Exhibit 2.) In response to the restriction requirement, Applicants elected the invention of the fusion protein in the '305 application and filed the instant application to pursue the non-elected invention (i.e., vectors, cells, and kits). Accordingly, Applicants submit that it is improper to now suggest that fusion proteins and vectors are "patentably indistinguishable subject matter."

With regard to the rejection of claims 5, 6, 8, 10, 12, 14, 15, and 17-19 being

obvious in view of claims 7, 8, 10-14, 16-18, and 20 of the '471 application. Applicants note that, on September 26, 2005, with the reply to the restriction requirement issued in connection with the '471 application, Applicants amended the claims in the '471 application. (A copy of the reply to restriction requirement and of the amended claims is enclosed as Exhibit 3.) The amended claims in the '471 application recite that the fusion protein includes (a) a ligand-binding domain of an erythropoietin receptor that associates when a ligand binds thereto and (b) a domain including a cytokine receptor or a proliferation inducing part thereof, that, upon association of the ligand-binding domain, imparts proliferation activity to a cell. Applicants submit that, in reference to the amended claims in the '471 application, it would not be obvious to one skilled in the art to substitute a ligand-binding domain of a steroid hormone receptor, as recited in the present claims, for the ligand-binding domain of an erythropoietin receptor. Applicants respectfully request that the Office reconsider the provisional obviousness-type double patenting rejection.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed are a Petition to extend the period for replying to the Office Action for three (3) months, to and including November 4, 2005, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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